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Case Report

Transarterial Chemoembolization-induced Tumor Lysis Syndrome: Different Results in the Same Hepatocellular Carcinoma Patient☆

Hsaing-Hung Lin [1, 3, 4 *], Wei-Ho Chang [2], Horng-Yuan Wang [1, 3, 4], Ming-Jen Chen [1, 3, 4], Shou-Chuan Shih [1, 3, 4]

[1] Division of Gastroenterology, Department of Internal Medicine, [2] Department of Family Medicine, Mackay Memorial Hospital, [3] Mackay Medical College, [4] Mackay Junior College of Medicine, Nursing and Management, Taipei City, Taiwan

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SUMMARY

Tumor lysis syndrome (TLS) is rarely induces after Transarterial chemoembolization for hepatocellular carcinoma. We present a patient with a large hepatocellular carcinoma who received twice transarterial embolization (TAE). Tumor lysis syndrome was induced after the first TACE in this patient. Due to the previous experience, precautionary measures were taken before the second TAE. Therefore no complications were noted afterwards. We should be aware of tumor lysis syndrome, especially in high risk patients.

1. Introduction

Tumor lysis syndrome (TLS) is a rare but potentially lethal complication that is induced after transarterial chemoembolization for hepatocelluar carcinoma (HCC). Only a few cases have been reported in the English-language literature. We present a patient with a large HCC who twice underwent transarterial embolization (TAE). To our knowledge, this is the first time that different results can be compared after the same patient had undergone two TAE procedures. Tumor lysis syndrome was induced in this patient after the first transcatheter arterial chemoembolization (TACE). The patient's renal functions improved after various treatments such as hemodialysis. Because of previous experience, precautionary measures were performed before the second TAE. No complications were noted afterwards. Physicians should be aware of TLS, especially in high-risk patients such as patients with large tumor burdens and/or rapidly dividing tumors, patients with a large number of ischemic areas within the tumor, patients with pretreatment renal dysfunction or volume depletion, and patients with severe postembolization syndrome.

2. Case report

A 65-year-old man had a past medical history of chronic hepatitis B and supraglottic cancer T3N0M0 post concurrent chemoradiation therapy; he had been in complete remission for 6 years. Multiple hepatic tumors were detected during routine abdominal ultrasonographic examination. No symptoms and signs such as abdominal pain, weight loss, general malaise, tea-colored urine, or jaundice were noted.

Laboratory data revealed a serum alpha-fetoprotein level of 1993.20 ng/dL; hemoglobin level of 12.5 g/dL; total leukocyte count of 4600/μL; platelet level of 161,000/μL; international normalized ratio (INR) of 1.31; serum total bilirubin level of 0.8 mg/dL; and albumin level of 3.5 g/dL. As for his renal function, the levels of blood urea nitrogen (21 mg/dL) and creatinine (1.3 mg/dL) were slightly elevated. The levels of sodium (139 mEq/L), potassium (3.7 mEq/L), and uric acid (6.9 mg/dL) were within normal limits. The degree of hepatic dysfunction was Child's classification A.

The abdominal ultrasound showed multiple hyperechoic masses, primarily in the right lobe of the liver. Abdominal dynamic computed tomography showed several nodular mass lesions varying in size over the right lobe of the liver; the largest mass

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* Correspondence to: Dr Hsiang-Hung Lin, MD, Division of Gastroenterology, Department of Internal Medicine, Mackay Memorial Hospital, Number 92, Section 2, Zhongshan North Road, Taipei City 10449, Taiwan.
E-mail address: malonegalisa@yahoo.com.tw (H.-H. Lin).

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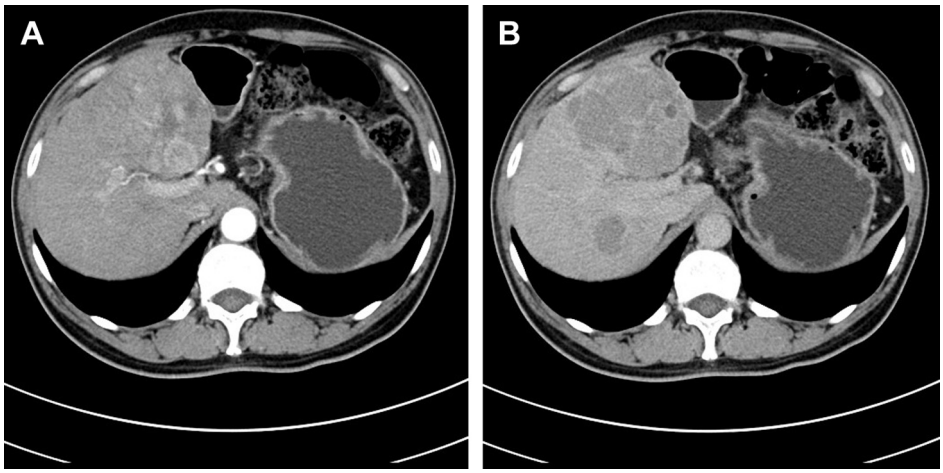

Fig. 1. Dynamic computed tomography (CT) images. (A) On the arterial phase image of the dynamic CT, several markedly enhanced masses are present and vary in size with the largest mass approximately 8.2 cm in diameter at S4 of the liver. The center of the tumor is not enhanced and is small necrotic tissue. (B) On the delayed-phase CT images, the tumor shows hypoattenuation.

measured approximately 8.2 cm in diameter in S4 of the liver (Fig. 1A and B). These tumors showed hypodensity on the precontrast film, faint hyperdensity in the arterial phase image, and hypodensity in the venous phase and delay-phase images. No evidence of portal vein thrombosis was demonstrated. Based on the laboratory data and various image findings, a diagnosis of HCC was clinically made. The stage of the tumor was Barcelona Clinic Liver Cancer (BCLC) stage B, Okuda stage II, Cancer of the Liver Italian Program (CLIP) stage 3, and TNM stage IIIA.

Based on the tumor stage, surgery and radiofrequency ablation did not seem applicable. In our institution, transarterial chemoembolization (TACE) is the first recommended therapy for patients with unresectable HCC. On June 22, 2012, the patient underwent the first TACE. Angiography revealed multiple hypervascular tumors supplied by bilateral hepatic arteries in both lobes of the liver. Therapeutic embolization was performed smoothly with mixed lipiodol (20 mL) and doxorubicin (40 mg), followed by gelfoam pieces and cephazolin at both hepatic arteries. Angiography obtained immediately after the TACE showed adequate occlusion of both hepatic arteries.

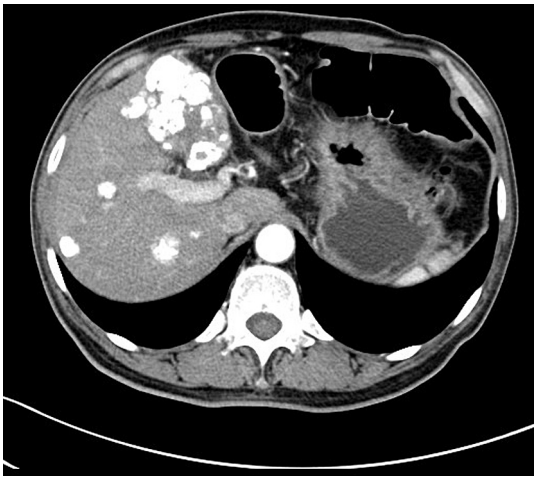

Fig. 2. The computed tomography images after the first transcatheter arterial chemoembolization (TACE) demonstrate good response to TACE with dense lipiodol retention. However, there is still marginal enhancement of the post-TACE lesion at S4 of the liver.

On the third day after the TACE procedure, the patient had fever, shortness of breath, and decreased urine output. Laboratory data revealed markedly deteriorated renal function. The levels of blood urea nitrogen (182 mg/dL), creatinine (15.2 mg), potassium (6.5 mEq/L), uric acid (9.1 mg/dL), and phosphate (6.2 mg/dL) were all markedly elevated. Hypocalcemia (7.1 mEq/L) was also noted. Thus, TLS was strongly suspected because of the presence of severe hyperuricemia, hyperkalemia, hypocalcemia, and acute renal failure, based on the Cairo–Bishop classification system. Hydration by intravenous fluid infusion and hemodialysis were performed immediately. The patient's renal functions improved and his urine output progressively increased after the treatments. He was discharged without any complications 19 days after the TACE procedure.

The patient's renal function fully recovered approximately two months after the first TACE. Follow-up abdominal dynamic computed tomography imaging demonstrated a good response to TACE with dense lipiodol retention. However, there was still marginal enhancement of the post-TACE lesion at S4 on the arterial enhancement image and decreased density on the delayed-phase image (Fig. 2). Therefore, a second TAE was arranged for a suspected residual hepatoma.

Because of previous experience, precautionary measures were performed at the time of the second TAE to prevent TLS. Adequate hydration by intravenous fluid infusion and acetylcysteine were administered before and after the second TAE. Superselective therapeutic embolization of the right branch of the left hepatic artery was performed smoothly using gelfoam pieces and cephazolin. After the procedure, his renal functions and electrolytes were all within normal limits. He was discharged 2 days after the second TAE without any complications.

3. Discussion

To our knowledge, this is the first time that different results can be compared after two TAE procedures on the same patient. Patients with large tumor sizes or rapidly dividing tumors are usually at greatest risk for TLS. There are other risk factors such as chemosensitive tumors; a large number of ischemic areas within a tumor; high levels of serum potassium, phosphate, uric acid, lacate, and lactate dehydrogenase; pretreatment renal dysfunction; and volume depletion[1-4]. Other major complications of TACE besides

TLS are liver dysfunction, severe postembolization syndrome, hepatic infarction, biloma formation, liver abscess, tumor rupture, septicemia, gastrointestinal bleeding, gallbladder infarction, splenic infarction, pulmonary oil embolism, and spinal cord injury[1,5,6].

A higher frequency of acute TLS tends to occur with hematological malignancies with high proliferative fractions, large bulky tumors such as Burkitt's lymphoma and other high grade non-Hodgkin's lymphoma, and acute leukemia and chronic leukemia[1]. However, other malignancies such as HCC, small-cell lung cancer, breast cancer, seminoma, metastatic medulloblastoma, and metastatic Meckel's cell tumor also reportedly cause TLS[4,7–12]. In our patient, a bulky tumor with a large number of ischemic areas after embolization and pretreatment renal dysfunction before the TAE probably enhanced the likelihood of TLS after the treatment.

Transcatheter arterial chemoembolization rarely induces TLS. To our knowledge, only a few cases have been reported in the English-language literature[13]. In 1998, Burney first reported two cases of TACE-induced TLS, both of which involved large HCCs (greater than 5 cm)[4]. Besides TACE, TLS has also been reported to occur after other treatments for HCC[13] such as radiofrequency ablation[14] and oral thalidomide[15].

We propose the following conclusions for why our patient had different adverse effects after the two episodes of TAE. First, the area of embolization between the two episodes varied greatly. In the first TACE, embolization was performed on both hepatic arteries, whereas superselective therapeutic embolization of the right branch of the left hepatic artery was performed for the second TAE. The area of embolization may be a major factor in deciding whether TLS will occur. Therefore, multiple TAEs should be arranged to prevent the possibility of TLS in patients with multiple hepatic tumors and pretreatment renal insufficiency. Second, adequate intravenous fluid hydration was not administered before and after the first TACE. The occurrence of post-TAE fever, TLS, and dehydration caused severe acute renal failure. Intravenous and oral N-acetylcysteine may prevent contrast-medium–induced nephropathy in patients treated with angioplasty[16]. Adequate hydration by intravenous fluid infusion and acetylcysteine were prescribed before and after the second TAE, thereby preventing TLS. Third, TACE with doxorubicin (40 mg) was performed in the first episode, whereas TAE was performed in the second episode. It remains unclear whether cytotoxicity, embolization, or both caused the metabolic abnormalities of TLS. However, direct cytotoxicity and ischemic necrosis of the tumor cells could have been contributing factors[4].

According to the most recent European Association for the Study of the Liver and European Organisation for Research And Treatment of Cancer (EASL-EORTC) practice guidelines, chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (EASL-EORTC 2012).[22] However, the optimal method or schedule remains undefined and the contribution of chemotherapy remains uncertain. Transcatheter arterial chemoembolization may be associated with a higher response rate, compared to TAE alone. However, the survival benefit of TACE over TAE remains unproven. The contribution of chemotherapy to the effectiveness of TACE has been questioned because HCC is relatively chemoresistant. An overall grade 3/4 toxicity occurred in 63.5% of individuals and in 83.7% of individuals in the TAE and TACE groups, respectively ($p = 0.019$)[17]. These severe constitutional adverse events and the use of nephrotoxic agents such as chemotherapeutic drugs may have a role in acute renal failure. Thus, we chose TAE as the subsequent treatment option.

The management of TLS depends on anticipation, prevention, and early recognition. In 2004, Cairo and Bishop defined a classification system in which TLS is classified as “laboratory TLS” or “clinical TLS”. A 25% change or a level above or below normal levels for any two or more serum values of uric acid (i.e., greater than 8 mg/dL), potassium (i.e., greater than 6 mEq/L), phosphate (i.e., greater than 4.5 mg/dL), and calcium (i.e., less than 7 mg/dL) within 7 days after cancer therapy would be classified as laboratory TLS. Laboratory TLS plus one or more of the following would be classified as clinical TLS: increased serum creatinine (i.e., 1.5 times the upper limit of normal), cardiac arrhythmia or sudden death, and seizure[18].

Therefore, close monitoring of renal functions and electrolytes in high-risk patients are needed. When TLS develops, effective treatments such as adequate hydration, oral medication (e.g., allopurinol and/or urate oxidase), or hemodialysis should be undertaken immediately.

Transarterial chemoembolization (TACE) is effective for HCC; however, acute renal failure developed in 12 (8.6%) of 140 patients after TACE. The risk factors included the number of treatment sessions; a Child–Pugh class B classification; and the development of severe postembolization syndrome, which is characterized by intermittent fever up to 38.1°C, ischemic hepatitis, abdominal pain, nausea, and loss of appetite[19]. Surgical resection is the treatment of choice for early stage HCC. The perioperative complications in elderly people receiving elective liver resection surgery did not differ markedly from these complications in younger patients. However, there was a higher incidence of postoperative respiratory complications in elderly patients, as indicated by a longer intubation time[20].

Most cancers occur in adults who are older than 65 years, and 70% of all cancer deaths are in this population. The increase in myeloproliferative and lymphoproliferative disorders and renal senescence may have a role in TLS in elderly patients. Age-related decreases in renin and aldosterone may contribute to an increased risk of hyperkalemia. The pathophysiology of acute and chronic renal failure in TLS involves many factors. Two major synergistic mechanisms are volume depletion and uric acid nephropathy. Numerous drugs taken by elderly patients may increase the risk of adverse drug interactions. Furthermore, many drugs can elevate the serum uric acid level, which leads to an increased risk of TLS. The management of TLS in elderly patients is often complicated by deteriorating renal and heart function, the presence of multiple comorbid conditions, polypharmacy, and difficulty in adhering to a complex medication regimen[21].

In conclusion, TAE-induced acute renal failure is common. Physicians should beware of TLS, especially in high-risk patients with large tumor burdens and/or rapidly dividing tumors, a large number of ischemic areas within the tumor, pretreatment renal dysfunction, volume depletion, and severe postembolization syndrome. Urine output, renal function, and electrolytes should be monitored closely after the TAE. Nephrotoxic agents such as aminoglycosides and nonsteroidal anti-inflammatory drugs should be avoided. If the clinical condition progresses to acute renal failure, aggressive hemodialysis should not be delayed to prevent irreversible renal damage or prevent life-threatening complications. The Institutional Review Board of the Mackay Memorial Hospital approved this case report (14MMHIS095).

References

1. Sakamoto N, Monzawa S, Nagano H, et al. Acute tumor lysis syndrome caused by transcatheter oily chemoembolization in a patient with a large hepatocellular carcinoma. *Cardiovasc Intervent Radiol*. 2007;30:508–511.
2. Sallan S. Pharmacoeconomic considerations in the management of acute tumor lysis syndrome. *Semin Oncol*. 2001;28(2 suppl 5):9–12.
3. Chasty RC, Liu-Yin JA. Acute tumour lysis syndrome. *Br J Hosp Med*. 1993;49:488–492.
4. Burney IA. Acute tumor lysis syndrome after transcatheter chemoembolization of hepatocellular carcinoma. *South Med J*. 1998;91:467–470.

5. Chung JW, Park JH, Im JG, et al. Pulmonary oil embolism after transcatheter oily chemoembolization of hepatocellular carcinoma. *Radiology*. 1993;187:689–693.
6. Chung JW, Park JH, Han JK, et al. Hepatic tumors: predisposing factors for complications of transcatheter oily chemoembolization. *Radiology*. 1996;198:33–40.
7. Drakos P, Bar-Ziv J, Catane R. Tumor lysis syndrome in nonhematologic malignancies. Report of a case and review of the literature. *Am J Clin Oncol*. 1994;17:502–505.
8. Barton JC. Tumor lysis syndrome in nonhematopoietic neoplasms. *Cancer*. 1989;64:738–740.
9. Vogelzang NJ, Nelimark RA, Nath KA. Tumor lysis syndrome after induction chemotherapy of small-cell bronchogenic carcinoma. *JAMA*. 1983;249:513–514.
10. Cech P, Block JB, Cone LA, et al. Tumor lysis syndrome after tamoxifen flare. *N Engl J Med*. 1986;315:263–264.
11. Oosterom A. Tumor lysis syndrome in a patient with metastatic Merkel cell carcinoma. *Cancer*. 1991;67:2207–2210.
12. Tomlinson GC, Solberg Jr LA. Acute tumor lysis syndrome with metastatic medulloblastoma. A case report. *Cancer*. 1984;53:1783–1785.
13. Hsieh PM, Hung KC, Chen YS. Tumor lysis syndrome after transarterial chemoembolization of hepatocellular carcinoma: case reports and literature review. *World J Gastroenterol*. 2009;15:4726–4728.
14. Lehner SG, Gould JE, Saad WE, et al. Tumor lysis syndrome after radiofrequency ablation of hepatocellular carcinoma. *AJR Am J Roentgenol*. 2005;185:1307–1309.
15. Lee CC, Wu YH, Chung SH, et al. Acute tumor lysis syndrome after thalidomide therapy in advanced hepatocellular carcinoma. *Oncologist*. 2006;11:87–88. author reply 89.
16. Marenzi G, Assanelli E, Marana I, et al. N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med*. 2006;354:2773–2782.
17. Meyer T, Kirkwood A, Roughton M, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolization vs embolization alone for hepatocellular carcinoma. *Br J Cancer*. 2013;108:1252–1259.
18. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. 2004;127:3–11.
19. Huo TI, Wu JC, Lee PC, et al. Incidence and risk factors for acute renal failure in patients with hepatocellular carcinoma undergoing transarterial chemoembolization: a prospective study. *Liver Int*. 2004;24:210–215.
20. Rau RH, Huang JY, Yang CL, et al. Perioperative complications of liver resection in the elderly with hepatocellular carcinoma: a comparison with younger patients. *Int J Gerontol*. 2009;3:101–107.
21. Pumo V, Sciacca D, Malaguarnera M. Tumor lysis syndrome in elderly. *Crit Rev Oncol Hematol*. 2007;64:31–42.
22. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56:908–943.